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## NUCLEAR STUDIES OF G INDUCED LOSS OF CONSCIOUSNESS (G-LOC)

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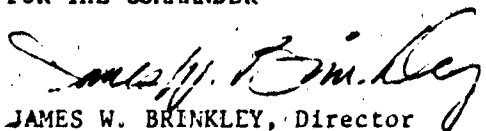
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The experiments reported herein were conducted according to the "Guide for the Care and Use of Laboratory Animals," Institute of Laboratory Animal Resources, National Research Council.

This report has been reviewed by the Office of Public Affairs (PA) and is releasable to the National Technical Information Service (NTIS). At NTIS, it will be available to the general public, including foreign nations.

This technical report has been reviewed and is approved for publication.

FOR THE COMMANDER

  
JAMES W. BRINKLEY, Director  
Biodynamics and Bioengineering Division  
Armstrong Laboratory

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13. ABSTRACT (Maximum 200 words) G-induced loss of consciousness or G-LOC has been attributed to 18 Class A mishaps (pilot deaths) in the Air Force since 1982. G-LOC is caused by a sudden, critical reduction of cerebral blood circulation caused by increased G force. Pilots undergoing lead-in fighter training at USAF centrifuge training facilities have experienced G-LOC during their training exposures to high sustained acceleration. Trainees are allowed to G-LOC twice in one day while undergoing training. Some trainees have experienced up to five G-LOCs in one day's training. The question arose whether or not repeated G-LOCs could develop cerebrovasculature sequelae, as there had been no reports of any medical consequences to G-LOC in over 50 years of aerospace medicine research. A primate model was used to study changes in fine anatomical brain structure as well as global blood flow, global blood volume, global oxygen metabolism, and glucose metabolism in the brain which occurred as a result of repeated G-LOC or exposure to 9 Gz. Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET) were used to obtain these measurements. Rhesus monkeys experienced +9 Gz briefly or until G-LOC four consecutive times under high Gz onset. Some animals were then scanned by MRI while others were analyzed using PET. MRI scans were negative; they showed no frontal lobe lesions or periventricular edema on any of the four animals.				
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analyzed. PET data demonstrated a decrease in global blood flow, global blood volume, global oxygen extraction ratio, global oxygen metabolism, and glucose metabolism in animals exposed to repeated G-LOC. In addition, blood flow in the gray matter of the brain was reduced below that found in the white matter. Control animals which experienced +Gz without G-LOC were shown to have decreased global blood flow but an increase in global blood volume, global oxygen extraction ratio, and global oxygen metabolism. All data were taken immediately to three hours after multiple G-LOC or Gz exposures. Despite these changes discovered during nuclear studies, there appears to be no permanent sequelae developed in the rhesus monkey as a result of the repeated exposures described here.

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## Preface

This report documents a series of experiments conducted under Project 7231 Task 35 Work Unit D2 entitled "G-induced Loss of Consciousness and Prophylaxis." The research was conducted in the Combined Stress Branch (AAMRL/BBS), Biodynamics and Bioengineering Division, Harry G. Armstrong Aerospace Medical Research Laboratory, Wright-Patterson AFB, OH. The research was funded by FY87 Laboratory Director's Funds.

The authors wish to extend their appreciation to Mr Marvin Roark (Raytheon Service Co.), who developed the acceleration profiles on the Dynamic Environment Simulator and to the rest of the Raytheon operations and maintenance crew including Greg Bathgate, Don McColler, Dick Szulewski and Bud Gould. The authors also acknowledge the contributions of TSgt Mike Swisher, SSgt Jim Swinhart, John Frazier and Tom Shriver, all of AAMRL/BBS.

Also acknowledged are the valuable contributions of the staffs at the 4950th Test Wing at Wright-Patterson AFB; Kettering Medical Center, Kettering, OH, where Nuclear Magnetic Resonance studies were conducted; and the University Hospital, Case Western Reserve University, Cleveland OH, where the Positron Emission Tomography studies were conducted. Finally, the authors wish to thank Vanessa Deer and Laura Sexton who typed this manuscript.

The animals used in this study were handled in accordance with the principles stated in the Guide for the Care and Use of Laboratory Animals, prepared by the Committee on Care and Uses of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council, DHHS, National Institute of Health Publication #85-23, 1985, and the Animal Welfare Act of 1966, as amended.

## TABLE OF CONTENTS

	PAGE
Introduction.....	1
Materials and Methods.....	2
Centrifuge.....	2
MRI and PET facilities.....	3
Subjects.....	3
Experimental design-MRI.....	3
Experimental design-PET.....	3
PET metabolic calculations.....	5
Results.....	5
Discussion.....	7
Conclusion.....	10
References.....	12
Appendix A.....	14

## LIST OF FIGURES

1. Dynamic Environment Simulator High G <sub>z</sub> Onset System.....	2
2. Blood Flow and Oxygen Analysis.....	6
3. G-LOC Model.....	9

## LIST OF TABLES

1. Sustained Acceleration History.....	4
2. Distribution of Blood Flow.....	5
3. Quantitative Analysis of Blood Flow and Oxygen Studies.....	6

## APPENDIX

A. Metabolic Calculations for Nuclear Study.....	14
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## INTRODUCTION

In modern high performance aircraft, Gz stress, which can sometimes lead to G induced loss of consciousness (G-LOC), is a real threat to pilot safety. G-LOC is a state of altered perception wherein one's awareness of reality is absent as a result of sudden, critical reduction of cerebral blood circulation caused by increased G force (5). Since 1982 there has been a total of 18 class A mishaps involving G-LOC, including 9 which occurred in the highly maneuverable F-16. A class A mishap is one which results in one million dollars or more damage to the aircraft or pilot death. From 1982 to 1988, G-LOC accounted for about 10% of all class A mission mishaps (2). Training the modern pilot to recognize and prevent G-LOC and to respond correctly to acceleration stress is therefore very important.

Since 1988, lead-in fighter training (LIFT) for Tactical Air Force crews has included centrifuge training at Holloman AFB, NM. At Holloman AFB, all candidate F-4/F-15/F-16 pilots must achieve straining, protected G tolerances up to 9 Gz. In attempting to pass this criterion in the past, at least 10% of all trainees lost consciousness (6); today, because of better training techniques, only about 6% of trainees experience G-LOC (8). If the trainee fails at achieving the 9 Gz exposure (or loses consciousness), he is allowed to repeat the exposure after a brief rest. Trainees currently are allowed to experience G-LOC two times in one day until they achieve 9 Gz (8). Prior to 1988, centrifuge, or high G training was conducted at the Air Force School of Aerospace Medicine (USAFSAM), Brooks AFB. During training on the centrifuge at USAFSAM, some trainees also experienced G-LOC. There is at least one reported incidence of allowing a trainee to G-LOC five times before discontinuing the high G training session (5). The question has been raised whether these repeated G-LOC episodes alter brain anatomy or cerebral metabolic functions of the pilot trainees in any way.

During G-LOC, a number of bodily functions may be monitored to evaluate the physiological effects of loss of consciousness. Electrocardiogram (EKG) profiles, during unconsciousness in general, are not altered beyond normal excessive G stress response (16). In the electroencephalogram (EEG) record, however, a distinct change in frequency from high (alpha) to low (delta) occurs during unconsciousness (9). In order to further study the effects of G-LOC at the molecular level in the brain, a novel approach was taken. Magnetic resonance imaging (MRI), which utilizes magnetic gradients to examine anatomical fine structure within the brain, was used to study the physical effects of repeated G-LOC (10). MRI is a proven imaging tool in modern radiology and allows a radiologist the opportunity of observing fine structures in the brain. To investigate the metabolic activities of the brain following unconsciousness, positron emission tomography (PET) was employed. PET detects gamma rays which result from the collision of a positron and an electron and uses these data to form a functional photographic

image and to generate specific calculations. The positron may be generated by the decay of an unstable isotope such as  $^{15}O$ ,  $^{11}C$ , or  $^{18}F$  which can be used to chemically modify a given tracer pharmaceutical. Through the use of these tracers and application of kinetic models, PET is used to measure regional blood flow, blood volume, oxygen extraction ratio, oxygen metabolism, glucose extraction ratio, and glucose metabolism. PET is a recent radiological development that does not produce the fine structure images as does MRI, but does present biochemical information that MRI cannot detect. Use of the PET has proven to be a valuable tool in identifying metabolic irregularities associated with G-LOC on a molecular level within the brain.

A primate whose physiology most closely resembles man was the most appropriate model for this investigation of G-LOC. A specially designed seat was available for use in subjecting the animals to high  $G_z$  onset rates using the man-rated centrifuge. MRI and PET facilities were available relatively nearby.

## MATERIALS AND METHODS

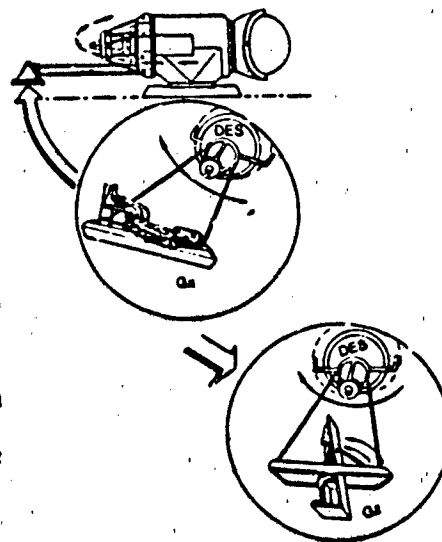
### Centrifuge

G stress was imposed using the Dynamic Environment Simulator (DES), a 3 axes, 19 foot radius, man-rated centrifuge located at the Armstrong Aerospace Medical Research Laboratory, Wright-Patterson AFB, Ohio (Figure 1). Rhesus monkeys were supported in a High G Onset (HIGON) chair in the supine position. The chair could be adjusted remotely to reposition the animal from the prone ( $+G_x$ ) to the upright seated ( $+G_z$ ) orientation in order to create rapid  $G_z$  onset (4). This technique for high  $G_z$  onset was required since the DES has a nominal 1 G/sec onset rate, and it was desired to expose the animals to high (7 G/sec) onset rates. Pilots flying high performance aircraft can experience high onset accelerations. The  $+G_x$  to  $+G_z$  maneuver emulated a high  $+G_z$  onset by converting the more tolerable  $+G_x$  exposure to the desired  $+G_z$  exposure.

Figure 1. Dynamic Environment Simulator  
High  $G_z$  Onset System

The method used to produce the rapid  $G_z$  onset rates required the centrifuge to achieve a predetermined rotation speed. The experimental platform was allowed to free swing so that the subject was in a  $G_x$  position (horizontal). Rapid  $G_z$  onset was produced by quickly uprighting the restraint chair to the  $G_z$  position (vertical).

Example: DES ARM SPEED	37 rpm
Equivalent G Field	9
Seat Pivot Duration	1.15 sec
$G_z$ Onset Rate	7
(in $G_z$ per sec)	



### MRI and PET Facilities

The 1.5 Tesla MRI facility was located at the Kettering Medical Center, Kettering, Ohio. The PET facility, containing a PET scanner with four rings of gamma ray detectors, was located at the University Hospital, Case Western Reserve University, Cleveland, Ohio.

### Subjects

Four Rhesus monkeys (*macaca mulatta*) were used in the MRI experiment and another eight Rhesus were used in the PET experiment. Heart rate was monitored during G stress using three EKG electrodes on the chest.

### Experimental Design - MRI

The animals were first taken to Kettering Medical Center for control MRI scans. Before scanning, the animals were anesthetized using ketamine hydrochloride since the animals needed to remain still for the MRI scans.

At the DES facility, the animals were first humanely restrained according to standard animal care protocol in the HIGON seat in the supine position on the centrifuge and fitted with three electrodes to monitor heart rate. They were then subjected to 0.2 G/sec acceleration onset from 1 to 9 G in the +G<sub>x</sub> (chest-to-back) direction. Once +9 G<sub>x</sub> was reached, the HIGON seat was remotely repositioned from prone to upright so that the animal experienced the exposure, as does a pilot, in a sitting orientation (+G<sub>z</sub>). Each animal was exposed to high G onset in the positive Z direction at +9 G<sub>z</sub> until G-LOC was determined to have occurred. Unconsciousness was determined by expert observers in the medical monitor's room who watched the animal via closed circuit television. The G<sub>z</sub> stress was terminated when G-LOC occurred. This procedure was repeated four times with a fifteen minute recovery period between each G-LOC episode. The animals were then immediately transported to the MRI facility for evaluation. There was an interval of about one hour after G exposure before MRI scanning was completed, due primarily to the ten mile trip from the DES facility to the MRI facility.

### Experimental Design - PET

During this phase of the experiment, the animals were first driven by van to the University Hospital in Cleveland, Ohio, to obtain baseline PET data on blood flow, blood volume, oxygen extraction ratio and oxygen metabolism; and in a separate experiment, glucose metabolism. The University Hospital PET facility was used because it was the nearest facility of its kind to Wright-Patterson AFB (approximately 250 miles). The animals were anesthetized with sodium pentobarbital. A cutdown of the femoral artery was performed to allow for on-line arterial blood sampling of PaO<sub>2</sub> and radioactivity. Three animals were used for the oxygen and blood flow data (M1, M2, and M3) while three

different animals were used for the glucose data (M4, M5, and M6). Glucose data on only one animal were calculated since only one animal had complete data. Two control animals (M7 and M8), which were subjected to +9 G<sub>z</sub> for a short period without losing consciousness (Table 1), were analyzed in an identical manner to the test animals M1, M2, and M3. The purpose of these two controls (M7, M8) was to determine whether observed differences in PET were due to the acceleration stress or G-LOC.

Blood and oxygen data were obtained using H<sub>2</sub><sup>15</sup>O as a positron emitting tracer. Preparation of the isotope was completed at the University Hospital using a 17 MeV cyclotron (22). <sup>18</sup>F was manufactured in a similar manner for use in labeling deoxyglucose in the sugar metabolism study (23).

The animals were taken to the centrifuge 10-14 days after the baseline data were collected, where they were exposed to G stress. The animals were continuously monitored by closed circuit television and accelerated in a manner identical to that described in the MRI experiment. Exposure periods for each animal are shown in Table 1.

TABLE 1. SUSTAINED ACCELERATION HISTORY (SEC)

	<u>O<sub>2</sub> + Blood Flow Study</u>			<u>Metabolism Study</u>			<u>O<sub>2</sub> Blood Flow Neg Controls</u>	
Trial	M1	M2	M3	M4	M5	M6	M7*	M8*
1	51	10	12	26	17	10	7	6
2	23	11	9	25	16	14	7	6
3	18	11	7	23	23	13	7	6
4	19	8	9	26	17	11	7	6
Total								
9G <sub>z</sub> Time	111	40	37	100	73	48	28	24
Avg Time to G-LOC or at 9G <sub>z</sub> :								
	28	10	9	25	18	12	7	6

\* - no G-LOC

Following the last exposure, the animals were flown by T-39 aircraft from Wright-Patterson AFB to Cleveland airport and then by helicopter to University Hospital where they received PET analysis approximately 2.5 to 3 hours after G-LOC exposure. In the glucose experiment, the animal was fitted with an intravenous catheter before G-stress was introduced. The radiolabelled 2-[<sup>18</sup>F]fluorodeoxyglucose (FDG) was then administered within 5 minutes after the last G stress exposure. Since <sup>18</sup>F has a half life of 110 minutes and the compound also requires approximately two hours to maintain a physiologically steady state within the tissue, it was administered before transport of the animal (23). The H<sub>2</sub><sup>15</sup>O was given in a bolus injection for the oxygen and blood flow studies at University Hospital and then the animal was scanned as soon as possible, since <sup>15</sup>O has a half life of only two minutes (22). Prior to pharmaceutical administration and scanning, the animals were anesthetized using sodium pentobarbital.

### Metabolic Calculations

In order to compute parameters for regional blood flow, blood volume, oxygen extraction ration, oxygen metabolism, and glucose metabolism, transfer functions have been developed at the PET facility (22,23,24). These computations are provided in Appendix A.

### RESULTS

From the MRI scans, one might expect to observe some periventricular edema (leakage of cerebrospinal fluid from the lateral ventricles into brain interstitial tissue) caused by compression of the brain under G stress. Edema was not detected, however. It was also anticipated that lesions on the frontal lobes may form as a result of repeated G-LOC exposure, based on reports from subjects who experienced repeated G-LOC exposures that "they did not feel right" for up to 24 hours after G-LOC (5). This also was not observed in the animals that experienced four consecutive G-LOCS. MRI scans were negative on all four animals.

The PET study, on the other hand, yielded some very interesting results. The six animals in the experimental group remained unconscious for approximately 5 to 10 seconds during each G-LOC exposure. Calculated blood flow in the white matter of the brain was relatively unchanged, whereas gray matter or cortical blood flow was markedly reduced three hours after repeated G-LOC (Table 2).

**TABLE 2. TISSUE DISTRIBUTION OF BLOOD FLOW**

	MONKEY 1			MONKEY 2			MONKEY 3		
	GRAY	WHITE	% DIFF	GRAY	WHITE	% DIFF	GRAY	WHITE	% DIFF
PRE-GLOC	59.7	58.4	-2.2	64.4	63.0	-2.2	61.6	57.3	-7.0
POST-GLOC	54.0	58.7	+8.7	53.6	64.4	+20.1	37.2	43.8	+17.7
TOTAL 9G EXPOSURE:	111 SECONDS			40 SECONDS			37 SECONDS		

Figure 2 Blood Flow and Oxygen Analysis

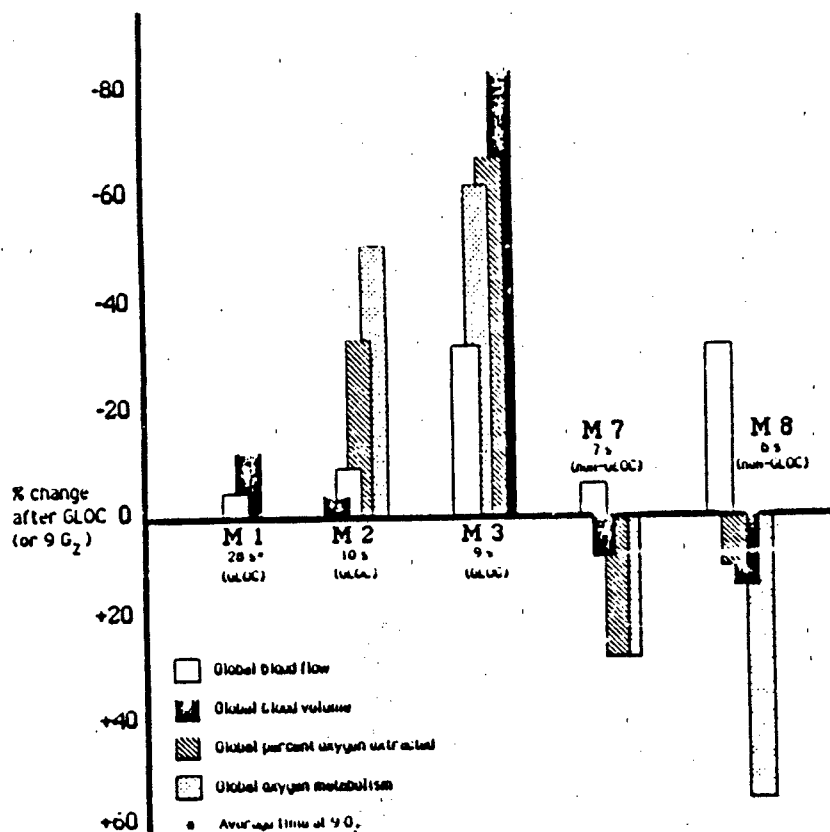


TABLE 3. QUANTITATIVE ANALYSIS OF BLOOD FLOW AND OXYGEN STUDIES

	MONKEY 1			MONKEY 2			MONKEY 3		
	PRE	POST	% CH	PRE	POST	% CH	PRE	POST	% CH
BRAIN BF	59.0	56.3	-4.6	64.1	58.8	-8.3	60.0	40.2+2.3*	-33.0
BRAIN BV	4.5	3.9	-13.3	4.8	4.6	-4.2	6.2	0.95	-84.7
BRIAN OE	41.7	N/A	—	43.1	28.4	-34.1	76.7	25.5	-66.8
BRIAN OM	3.0	N/A	—	3.2	1.5	-53.1	3.7	1.4	-62.2
TOTAL 9G EXPOSURE:	111 SECONDS			40 SECONDS			37 SECONDS		
BF: GLOBAL BLOOD FLOW IN ml/100g/min									
BV: GLOBAL BLOOD VOLUME IN ml/100g									
OE: GLOBAL PERCENT OXYGEN EXTRACTED									
OM: GLOBAL OXYGEN METABOLISM IN ml/100g/min									
* : AVERAGE OF 4 BF <sub>s</sub>									

Global blood flow as well as blood volume, global percent oxygen extraction ratio and oxygen metabolism were markedly reduced in M1, M2, and M3 who received repeated G-LOC; whereas M7 and M8, who experienced 9 Gz briefly without G-LOC, were able to compensate for decreased blood flow with increased blood volume, oxygen extraction and oxygen metabolism (Figure 2, Table 3). In addition, glucose metabolism was decreased by 50% after G-LOC in the one animal which was analyzed. All animals survived the G exposures, MRI, and PET analyses without sequelae and were returned to the vivarium. No aftereffects or long-term sequelae due to the exposures were observed in any of the animals.

#### DISCUSSION

Since the results of the MRI study showed no anatomical irregularity or lesions following repeated G-LOC, it may be concluded that the intercranial pressures associated with G stress in these exposures were not sufficient to cause harm. In a recent Navy study, human subjects who experienced G-LOC four times over a period of two weeks also did not display any negative effects under MRI analysis (19). However, it is possible that the level of MRI scanning resolution was not fine enough to detect damage. Techniques are currently being developed which utilize Nuclear Magnetic Resonance spectra obtained by MRI from a single, specific area in the brain. When these spectra are compared with a control area, differences in atomic composition of the two areas may be detected (10). Use of this technique in the future may aid in detection of anatomical changes induced by G stress, if there are any.

The results of the PET study demonstrate a definite difference between baseline and post G-LOC data in a number of areas. Decreased blood flow to the gray matter of the brain following G-LOC has some interesting implications. White matter consists mainly of axons and contains few capillaries so maintenance of blood flow is not very critical. Gray matter consists of nerve cell bodies and their dendrites which are responsible for origination of neuronal action potentials and nerve cell metabolism (3). The gray matter also contains astrocytes which aid nerve cells by integrating function and by acting as an intermediary between circulating blood and nerve cells (3). Reduced blood flow to cortical tissue, if not counteracted by blood pooling and increased cellular efficiency in obtaining critical nutrients from the blood, could have detrimental effects on cognitive functions. According to this study, these effects may be observed in primates up to three hours after a series of four G-LOC episodes. The decrease in blood flow observed in the gray matter of the brain cannot be drawn on as definitive data from this investigation, however, since there was no analysis of this sort in animals subjected to 9 Gz without G-LOC.

There is also variance between G-LOC and non G-LOC data concerning blood volume, oxygen extraction ratio, and oxygen metabolism in the brain. Global blood flow is reduced in the animals exposed to 9 Gz without G-LOC in a manner similar to the

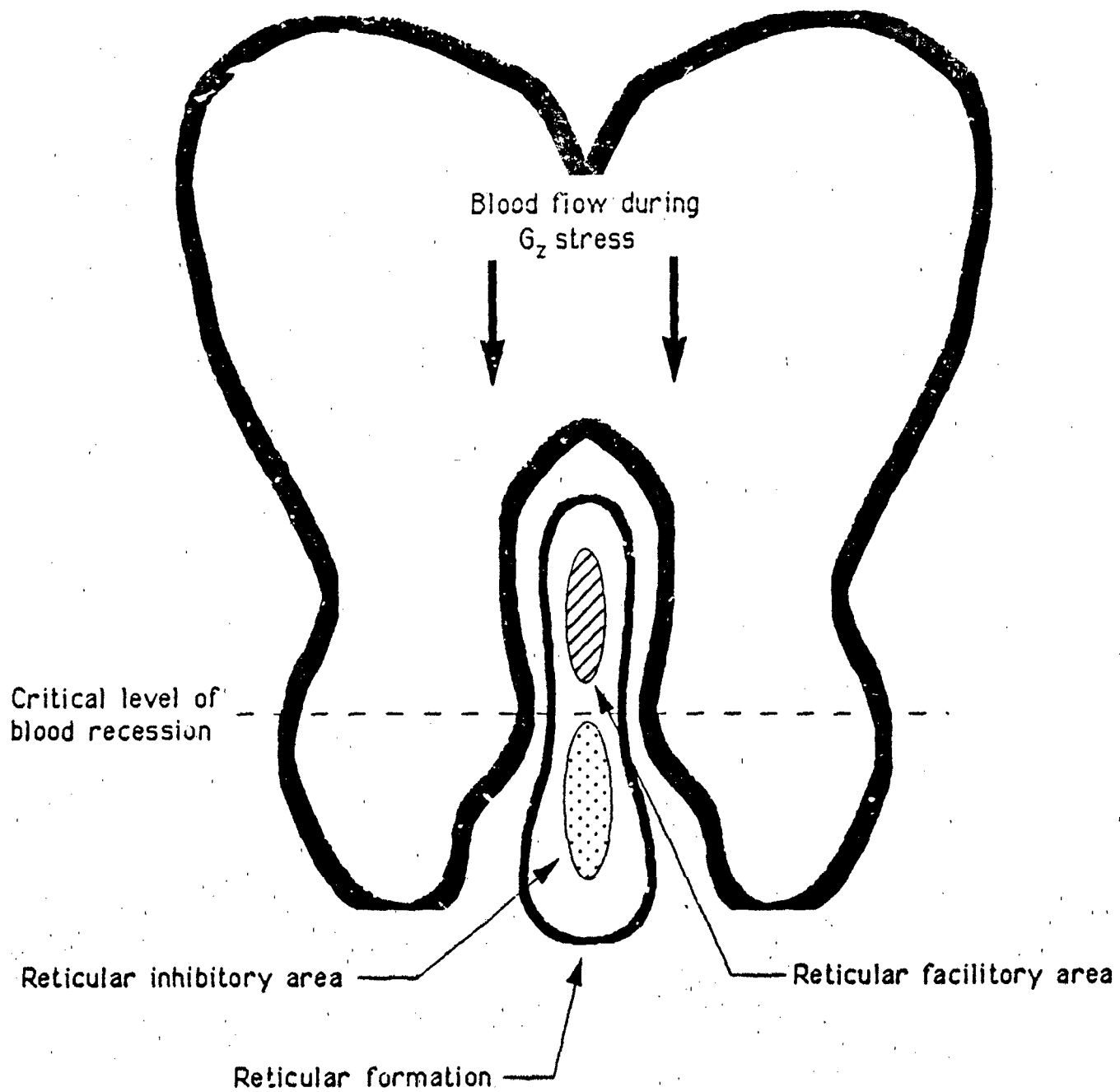
G-LOC exposed animals. Since, during Gz stress, blood is theoretically forced out of the head toward the lower extremities, this finding is not surprising. However, the non G-LOC controls show a concomitant elevation in blood volume which is a normal physiological response to decreased blood flow (12). The G-LOC animals did not display this response for unknown reasons. In addition, the G-LOC animals showed a large decrease in oxygen metabolism and oxygen extraction ratio. According to some pathological examples (11), reduced blood flow to the brain should result in a positive compensation in oxygen extraction ratio and metabolism to maintain cellular homeostasis, as seen in the control 9 Gz animals. In other clinical examples, cellular metabolism is decreased under hypoxia or conditions where blood pressure is lower than 70 mmHg as observed in the G-LOC animals (1).

In related research at the the U.S. Air Force School of Aerospace Medicine, it has been shown that there is no change in neuronal adenosinetriphosphate (ATP) content immediately following G-LOC, but a decrease is observed one hour following G-LOC in rats (10). This result is consistent with observations of slowed brain activity (low frequency delta waves) during G-LOC which is followed by an abrupt increase in activity that accompanies the regaining of consciousness. However, this reduction of ATP content after G-LOC should cause the cell to increase glucose metabolism and oxygen uptake which leads to ATP production unless there is a decrease in neuronal activity or a specific signal present down-regulating metabolic processes.

The data inferring a general decrease in energy production is supported by the reduction in glucose metabolism observed in the one animal that was sampled. The G-LOC or increased time at Gz may cause some long-lasting disruption in energy production. From a functional standpoint, such a decrease in energy production in the cortical tissue of the brain could contribute to impairment of cognitive functioning, which, according to this study, could last up to three hours after repeated incidence of G-LOC. If this observation is subsequently supported with additional metabolic studies, it may have an impact on current policies governing the temporary grounding of pilots who experience G-LOC.

J. Whinnery's model of events in the brain that lead to G-LOC (17) may help explain the basis of the metabolic changes seen in this study and others (15). His theory, which is derived from the field of sleep research, points to the inhibitory region of the reticular formation (raphe nuclei) as the key to many symptoms of G-LOC. According to his model, as a subject is exposed to high G-onset, blood flow is reduced first in the outer cerebral cortex and in a step-wise fashion through the brain down to the reticular formation, until unconsciousness results (Figure 3). Since the low frequency delta waves associated with sleep are present during G-LOC, the reticular formation may be exerting its control over the cortex. In addition, it is known that when the reticular formation does not receive sufficient blood flow, unconsciousness and a sleep-like state result (13).

Figure 3      G-LOC model (Ref 17)



Since the reticular formation is known to also influence homeostatic mechanisms of the neuraxis (3), Whinnery's theory may explain some of the PET metabolic data. Signals (specific neurotransmitters) from the reticular inhibitory area under G-stress, which induce sleep-like activities, may also be involved in regulating metabolic activities of the brain during and after G-LOC. It may be hypothesized that, at first under G stress, the cortical neurons themselves respond to ischemia/hypoxia by increasing their oxygen extraction ratio and oxygen metabolism (Figure 2), which is consistent with pathological examples (11, 22, 23). However, over a longer period of time and G stress, as normal blood perfusion recedes to the level of the reticular inhibitory area (characterized by G-LOC) signals may be sent by the reticular formation, that is now uninhibited by the cortex, which significantly down-regulate the metabolic machinery of the neurons in an effort to preserve what metabolites (ATP) are present in a perceived acute ischemic attack. This may manifest itself in lowered glucose metabolism, lowered oxygen extraction ratio, and oxygen metabolism as seen in this study up to three hours after G stress episodes (Figure 2). This decrease in essential metabolite uptake may contribute to the decreased levels of ATP, mentioned above, observed one hour following G-LOC. Since the reticular formation projects its associated axons to many parts of the brain, all areas may be affected.

Additional investigation is necessary to confirm the results generated from this small subject pool to obtain more statistically meaningful data. PET scanning at longer as well as shorter intervals after G-LOC exposure could be used to determine the duration of the metabolic responses noted in this study. New PET techniques involving biodegradable microspheres containing long-lived isotopes could be used to obtain regional blood flow data reflecting values present minutes after G exposure (12). Data obtained from additional trials (more than four) of G-LOC in individual animals versus few G-LOC trials (less than four) could be used to examine attenuation of neuronal metabolic responses to G-LOC exposure. Such data could be used as an index of pilot performance capabilities after an incidence of G-LOC.

#### CONCLUSIONS

There appears to be no evidence of permanent sequelae resulting from G-LOC. Scientific as well as anecdotal evidence supports this observation. Dr Earl Wood, during his acceleration research at the Mayo Clinic, lost consciousness (G-LOC) 9 times and experienced many blackouts over a period of 5 years (1942-1946). Dr Wood, at the age of 78, is still active today, reports no apparent sequelae from his numerous G-LOC exposures, and remains a part-time active researcher at the Mayo Clinic (21). Dr Ed Lambert, a co-investigator with Wood, lost consciousness 23 times during the same time period on the Mayo Centrifuge. Lambert, at age 75, is still an active researcher at the University of Minnesota's Department of Neurology (21).

Cellular research at the USAFSAM directed toward the biochemistry of G-LOC will shed light on the etiology of G-LOC (15). Human G-LOC studies at the Naval Air Development Center have uncovered a

previously unobserved phenomenon termed "almost unconscious" wherein the centrifuge subject does not experience the classic total incapacitation periods previously described for G-LOC (15). Research will continue at both the cellular and operational levels in an effort to solve one of the most serious human factors problems facing pilots of high performance aircraft, G-LOC.

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## APPENDIX A

### Metabolic Calculations for Nuclear Study

In order to compute parameters for regional blood flow, blood volume, oxygen extraction ration, oxygen metabolism, and glucose metabolism, transfer functions have been developed at the PET facility (22, 23, 24). Equation A-1 describes the basic elements of the blood flow model where the concentration of radioactivity in the tissue over time equals a function of the radioactivity in the venous blood that flows out over time subtracted from the radioactivity concentration of the arterial blood that flows in over time, where  $f$  is the flow per unit weight of tissue (7, 14).

$$\frac{dC(t)}{dt} = fC_a(t) - fC_v(t) \quad \text{Eqn A-1}$$

$$= fC_a(t) - \frac{f}{\lambda} C(t) \quad \text{Eqn A-2}$$

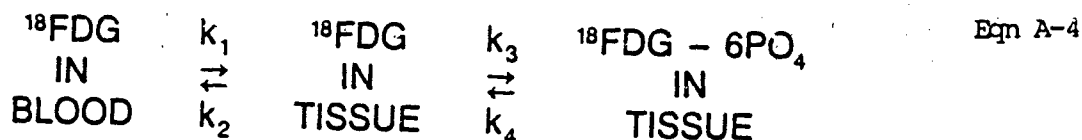
$$\lambda = \frac{\text{PARTITION COEFFICIENT}}{C(t)/C_v(t)}$$

Regional cerebral blood flow,  $f$ , may be computed from equation A-2.  $C$  represents a sum over time,  $T$ , of local tissue radiotracer concentration as measured by the PET scanner;  $\lambda$  is the partition coefficient of the blood brain barrier; and  $C_a(T)^*$  is the concentration of radiotracer in arterial blood at a single time,  $T$ . The asterisk indicates the operation of convolution.

$$C = f \int_0^T C_a(T)^* \exp \left[ -\left( \frac{f}{\lambda} \right) T \right] dT \quad \text{Eqn A-3}$$

Glucose metabolism data represent an integral of metabolism over a three hour period after repeated G-LOC since  $^{18}\text{FDG-6}$  phosphate can be dephosphorylated via hexokinase.  $^{18}\text{FDG-6PO}_4$  accumulates in the tissue and does not proceed toward energy production nor is it converted to glycogen for energy storage since it contains fluorine rather than a hydroxyl group in its second carbon atom.

In order to calculate Local Cerebral Metabolic Rate of Glucose (LCMRG), an evaluation of the time course kinetics of the 3-compartment model (24), where  $k_i$  is a rate constant, of FDG in plasma to tissue and from tissue to FDG-6PO<sub>4</sub> (see equation A-4) is necessary.



After lengthy derivation, equation 5 may be used to calculate LCMRG (23). The first term in the numerator refers to FDG-6PO<sub>4</sub> total radiation in the tissue at time, T. The second term refers to the FDG precursor contained in the tissue as a function of time t. The terms in the denominator correct for isotope effect and lag in tissue equilibration with plasma.

$$\text{LCMRG} = \frac{C_i^*(T) - k_i^* e^{-(k_2^* + k_3^*)T} \int_0^T C_p^* e^{(k_2^* + k_3^*)t} dt}{\left[ \frac{\lambda \cdot V_m^* \cdot K_m}{\phi \cdot V_m \cdot K_m} \right] \left[ \int_0^T \left( \frac{C_p^*}{C_p} \right) dt - e^{-(k_2^* + k_3^*)T} \int_0^T \left( \frac{C_p^*}{C_p} \right) e^{(k_2^* + k_3^*)t} dt \right]}
 \quad \text{Eqn A-5}$$

END

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1-92